claims 4, 7, 9, 11 and 15-19 will be pending in the application.

Applicant will discuss the amendments in detail in connection with the Examiner's rejections. None of the amendments introduces new matter. Applicant requests entry of the amendments and reconsideration of the pending claims.

Notice to Comply with Sequence Listing Rules

Applicant received a Notice To Comply With Sequence Rules 37 C.F.R. §§ 1.821-1.825 ("Notice") in the above-identified application (copy enclosed). The Examiner states that the application, as filed, contains sequences that do not appear in the previously filed Sequence Listings. The Notice states that applicant must provide a substitute Sequence Listing (on paper and a computer readable form), an amendment directing its entry of the substitute Sequence Listing into the specification and a Statement that the content of the paper and computer readable copies is the same and includes no new matter.

Accordingly, applicants enclose substitute Sequence Listing pages 1-13, a Computer Readable Form submission of same and the required Statements.

Information Disclosure Statement

The Examiner states that copies of the documents made of record by applicant in this application in the paper filed March 11, 1999 and listed on the Form PTO-1449 filed on that date appear not to have been filed.

Accordingly applicant submits herewith a copy of the previously filed Form PTO-1449 and copies of the documents listed thereon. Applicant requests that the cited documents be (1) fully considered by the Examiner during the course of

examination of this application and (2) printed on any patent issuing from this application.

Examiner's Objections

Claims 4, 6, 7, 9-12 an 14-16 stand objected to as lacking an introductory indefinite article. Claims 6, 7, 10-12 and 14-16 further stand objected to as depending from non-elected claims or reciting subject matter other than the elected invention, viral proteins of the invention and compositions and methods comprising such proteins. Applicant's cancellation of claims 6, 10, 12 and 14, without prejudice, obviates the objection as to those claims.

Applicant has amended claims 4, 7, 9, 11 and 15-16 to include an introductory indefinite article and claims 7 and 9 to correct their dependency. Applicant has amended claims 7, 11, 15 and 16 to remove non-elected subject matter.

Rejections Under 35 U.S.C. § 112, Second Paragraph and § 101

Claims 4, 6, 7, 9-12 and 14-16 stand rejected under 35 U.S.C. § 112, second paragraph, as "indefinite" for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Within respect to claim 4, the Examiner states that the term "homologous sequences having at least 75% homology to SEQ ID NO: 4" is unclear since neither "homologous sequences" nor "homology" has been defined in the specification such that one of skill in the art could reasonably determine what applicant intends by cited terminology (Office Action, pp. 3, lines 18-24; pp. 4, lines 1-2). Applicant respectfully traverses.

The specification states that the amino acid homology in the non-coding region of different picornavirus

isolates was established by screening the entire Swiss Protein Data Bank using the BLITZ search algorithm with standard search parameters (Office Action, pp. 12, lines 12-15). The specification also recites that "the BLITZ search algorithm takes into account identical as well as similar amino acids" (Office Action, pp. 10, lines 5-6). Thus, one skilled in the art would understand what is meant by "homologous sequence" or "homology" in the claims.

With respect to claim 6, the Examiner contends that the term "at least a part of a structural protein" is indefinite since a part of a protein can be as little as a single amino acid. Applicant's cancellation of claim 6, without prejudice, obviates this rejection.

The Examiner asserts that claims 9 and 14 are "indefinite" because they depend from non-elected claims 8 and 13, respectively. Applicant's cancellation of claim 14, without prejudice, obviates the rejection as to that claim. Claim 9, as amended, no longer refers to a non-elected claim.

Claims 11 and 12 stand rejected under § 112, second paragraph, as "indefinite" and under 35 U.S.C. § 101 as an improper process claim. Specifically, in the Examiner's view, the claims recite a use without any positive method steps. Applicant's cancellation of claim 12, without prejudice, obviates the rejection as to that claim. Claim 11, as amended, is directed to a pharmaceutical composition (medicament) comprising a viral protein of the invention. Support for the amendment may be found in claims 11 and 12 as originally filed.

In view of the foregoing, applicant requests withdrawal of the rejections under 35 U.S.C. § 112, second paragraph and § 101.

Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 4, 6 and 7 stand rejected under 35 U.S.C. § 112, first paragraph, as not enabled. Specifically, the Examiner asserts that the application, as filed, does not teach how to make and use proteins "having at least 75% homology" SEQ ID NO: 4 or which fragments thereof are antigenic. Finally, in the Examiner's view, the application, as filed, does not teach how to make and use and antigen that is "at least a part of a structural protein". Applicant's cancellation of claim 6, without prejudice, obviates the rejection as to that claim. In view of the amendments to claims 4 and 7, applicant traverses.

Claim 4 refers in relevant part to a protein comprising an amino acid sequence having at least 75% homology with SEQ ID NO: 4. As discussed above, the application, as filed, refers to at least one algorithm (BLITZ) for determining amino acid sequence homology. Accordingly, one of ordinary skill in the art would readily be able to make and use proteins at least 75% homologous in amino acid sequence to SEQ ID NO: 4 without undue experimentation.

Claim 7, as amended, no longer contains the phrase "at least a part" of an antigen protein. Instead, the claim refers to a diagnostic kit comprising a protein according to claim 4 or claim 17 (a protein comprising an antigen). The application as filed teaches a method for determining if a protein of the invention or a fragment thereof is antigenic.

Page 4, line 30, to page 5, line 14, describes "Antisera and Serological Procedures". Specifically, the application, as filed, describes immunizing an animal, collecting serum from the immunized animal and determining the antibody titer to the immunogen using an indirect immunofluorescence test (IFT). Accordingly, one of ordinary

skill in the art could readily determine if any particular protein of the invention or fragment thereof is an antigen. Accordingly, claims 4 and 7 are fully enabled by the application, as filed.

Claims 9-12 and 14-16 stand rejected under 35 U.S.C. §§ 112, first paragraph, as non-enabled. Specifically, the Examiner alleges that claims 9-12 and 14-16 are drawn to claims involving vaccines or treatments for diseases or conditions that may be caused by the Ljungan virus. The Examiner contends that the specification does not provide factual evidence that any known diseases or pathological conditions are in fact caused by the Ljungan virus. Applicant's cancellation of claims 10, 12 and 14, without prejudice, obviates the rejection as to those claims. As to claims 9, 11, 15 and 16, applicant respectfully traverses.

Claim 9, as amended, is directed to a vaccine comprising a protein according to claim 4 or claim 17. Claim 11, as amended, is directed to a pharmaceutical composition for treating or preventing infection by a virus of the invention. Claim 15, as amended, is directed to a vaccine comprising a protein according to claim 4 or claim 17. Claim 16, as amended, is directed to a method for preventing or treating infection by a virus of the invention.

The application, as filed, provides factual evidence of human infection by a virus of the invention. Specifically, at page 14, lines 1-28, describes human sera containing antibodies specific for the viral proteins of the invention. Those sera were collected from patients diagnosed with diabetes mellitus or myocarditis.

Further, the specification, as filed, states: "Infection with TMEV and EMCV have provided excellent animal models for inducing myocarditis, diabetes mellitus and

different neurological disorders such as demyelinating diseases resembling multiple sclerosis in mice (refs 10-16). Other neurological or muscular disorders in which a picoviral infection is suspected to be the triggering factor and in which there is also an autoimmune component are Cardiomyopathia, Multiple Sclerosis (MS), Chronic Fatigue Syndrome (CFS), Myasthenia Gravis (MG), and Amyothrophic Lateral Sclerosis (ALS)." (pp. 3, lines 4-11).

Certain listed references in the PTO-1449 which have not yet been considered by the Examiner and which are enclosed with this response describe known diseases or pathological conditions caused by the Ljungan virus.

For example, Jun et al. (Journal of General Virology 76: 2557-2566, 1995) teaches that the EMC virus, a member of the picornavirus family, can induce diabetes. Dan et al. (Experimental Animal 44(3): 211-218, 1995) also describes a new variant of the EMC virus (DK-27) which can induce diabetes mellitus. Tolbert et al. (Proc. Soc. Exp. Biol. Med. 205(2): 124, 1994) reports that the D variant of the EMC virus can be used to induce acute-onset diabetes mellitus and myocarditis as well as establishing a murine model for the study of chronic pancreatitis and heart-valve disease.

Consequently, the applicant argues that the specification and cited documents in the PTO-1449 enables one skilled in the art to make and use the invention with respect to vaccines and treatments for infection by a virus of the invention.

Accordingly, applicant requests that the rejections under 35 U.S.C. § 112, first paragraph, be withdrawn.

Applicants believe that in view of the foregoing, the claims are in condition for allowance. Accordingly, applicants request that the Examiner enter the amendments

presented herein, consider the foregoing remarks and allow the pending claims to issue.

Respectfully submitted,

Jane T. Gunnison

Jane T. Gunnison (Reg. No. 38,479)
Attorney for Applicant
c/o FISH & NEAVE
1251 Avenue of the Americas
New York, New York 10020-1104
Tel.: (212) 596-9000

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APRIL 16, 2001

CONNIE WONG

Name of person signing

Connie Wong

Signature of person signing

APPENDIX A

4. (Amended) A protein [Protein] comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 4 (partial structural protein of Ljungan 145SL)

Lys Asp Leu Met Glu Ile Ala Arg Met Pro Ser Val Tyr Lys Gly Glu
5 10 15
Arg Thr Glu Pro Gly Gly Thr Asn Gly Tyr Phe Gln Trp Ser His Thr
20 25 30
His Ser Pro Ile Asn Trp Val Phe Asp Gly Gly Ile His Leu Glu Asp
35 40 45
Met Pro Asn Leu Asn Leu Phe Ser Ser Cys Tyr Asn Tyr Trp Arg Gly
50 55 60
Ser Thr Val Leu Lys Leu Thr Val Tyr Ala Ser Thr Phe Asn Lys Gly
65 70 75 80
Arg Leu Arg Met Ala Phe Phe Pro Ile Met Met Gln Gly Thr Gln Arg
85 90 95
Lys Lys His Lys Cys Leu Phe Met Val Cys Asp Ile Gly Leu Asn Asn
100 105 110
Thr Phe Glu Met Thr Ile Pro Tyr Thr Trp Gly Asn Trp Met Arg Pro
115 120 125
Thr Arg Gly Ser Val Ile Gly Trp Leu Arg Ile Asp Val Leu Asn Arg
130 135 140
Leu Thr Tyr Asn Ser Ser Ser Pro Asn Ala Val Asn Cys Ile Leu Gln
145 150 155 160
Val Lys Met Gly Asn Asp Ala Lys Phe Met Val Pro Thr Thr Ser Asn
165 170 175
Ile Val Trp ,

and homologous sequences having at least 75% homology to the SEQ ID NO: 4, and antigenic fragments of the sequences.

[6. Antigen comprising at least a part of a structural protein of the picornavirus according to claim 1.]

7. (Twice amended) [Diagnostic] A diagnostic kit comprising [at least one member from the group consisting of an antiserum or antibody or an antigen-binding part thereof, an antigen] a protein according to claim [6] 4 or claim 17 or an antibody-binding part thereof. [, one or several probes designed with respect to the genome of the virus and one or several primers designed with respect to the genome of the virus.]

9. (Amended) The vaccine [Vaccine] according to [claim 8] claim 15 or 18 which additionally comprises an adjuvant.

[10. Ljungan picornavirus according to claim 1, optionally in attenuated or killed form, an antiserum or antibody or an antigen for use in a medicament.]

11. (Twice amended) A pharmaceutical composition for treating or preventing infection by a virus in a mammal, said virus comprising in the non-coding region of its viral genome a nucleotide sequence corresponding to a cDNA sequence selected from the group consisting of SEQ ID NO: 1 and sequences at least 75% homologous to SEQ ID NO: 1, [Use of a Ljungan picornavirus according to claim 1, optionally in attenuated or killed form, an antiserum or antibody or an antigen] said pharmaceutical composition comprising a protein according to claim 4 or claim 17 or an antibody-

binding part thereof.[, in the preparation of a medicament for prophylactic or therapeutic treatment of a disease caused by said virus.]

[12. Use according to claim 11, wherein the disease caused by said virus is one of Myocarditis, Cardiomyopathia, Guillain Barré Syndrome, and Diabetes Mellitus, Multiple Sclerosis, Chronic Fatigue Syndrome, Myasthenia Gravis, Amyothrophic Lateral Sclerosis, Dermatomyositis, Polymyositis, Spontaneous Abortion, and Sudden Infant Death Syndrome.]

[14. Method according to claim 13, wherein the disease caused by said virus is one of Myocarditis, Cardiomyopathia, Guillain Barré Syndrome, and Diabetes Mellitus, Multiple Sclerosis, Chronic Fatigue Syndrome, Myasthenia Gravis, Amyothrophic Lateral Sclerosis, Dermatomyositis, Polymyositis, Spontaneous Abortion, and Sudden Infant Death Syndrome.]

15. (Amended) [Vaccine] A vaccine having as an immunizing or neutralizing component a [member selected from the group consisting of a) the virus according to claim 1, and DNA corresponding to the genomic RNA of the virus] protein according to claim 4 or claim 17 or an antibody-binding part thereof.

16. (Amended) [Method of prophylactic or therapeutic treatment of a disease] A method for preventin or treating infection in a mammal, including a human, [caused] by a virus comprising in the non-coding region of its viral genome a nucleotide sequence corresponding to a cDNA sequence selected from the group consisting of SEQ ID NO: 1 and sequences at least 75% homologous to SEQ ID NO: 1,

[according to claim 1 in a mammal, including human, which comprises] said method comprising administering to said mammal a prophylactically or therapeutically effective amount of a [medicament comprising as an active ingredient a member of the group consisting of the virus according to claim 1, an antigen including a subunit of the virus, and DNA corresponding to the genomic RNA of the virus] composition selected from the group consisting of:

(a) a protein according to claim 4 or claim 17 or an antibody-binding part thereof;

(b) a pharmaceutical composition according to claim 11; and

(c) a vaccine according to any one of claims 9, 15 or 18.

17. A protein according to claim 4, comprising an antigen.

18. The vaccine according to claim 15, said vaccine additionally comprising a subunit of a virus, said virus comprising in the non-coding region of its viral genome a nucleotide sequence corresponding to a cDNA sequence selected from the group consisting of SEQ ID NO: 1 and sequences at least 75% homologous to SEQ ID NO: 1.

19. The method according to claim 16, wherein the pharmaceutical composition additionally comprises a subunit of the virus.